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THE MADRAS CLINICAL JOURNAL

JOURNAL OF THE MADRAS STATE BRANCH OF THE INDIAN MEDICAL ASSOCIATION

(With which is incorporated the "Miscellany")

Vol. XXIV] APRIL 1958 [No. 10

GITALIN: A CARDIAC GLYCOSIDE WITH WIDE THERAPEUTIC RANGE

By

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EVER since William Withering introduced foxglove, one of the components of the twenty or more herbs used by an old woman of Shropshire 'for the cure of the dropsy', medical men have studied its effects both in the clinic and the laboratory. Even in those days it was noted for the violent vomiting and purging it produced, though its diuretic property was first described by Withering[8]. The leaves of the red foxglove (Digitalis purpurea) have been subjected to intensive studies in the laboratory resulting in the isolation of the three glycosides, digitoxin, gitoxin and gitalin in the chemically pure state.

The powdered leaf of Digitalis purpurea and the tincture occupied the pride of place in the therapy of cardiac failure till recently, when the purified glycosides became available. All the available preparations then, were found to produce pronounced clinical benefit. There was one disadvantage however, and that was the production of toxic symptoms in a number of patients. Many pharmacologists believe that the toxic properties of the digitalis glycosides are only an extension of their therapeutic properties. Friedberg [5] mentions that the absence of any toxic effects with a digitalis preparation is evidence of its inertness. It was found that the therapeutic dose of any digitalis preparation was close to its toxic dose. Under certain circumstances the toxic dose was even lower than the dose required to produce any therapeutic benefit, thus rendering digitalization impossible. In order to get a preparation with a wider margin of safety many cardiac glycosides were investigated.

One approach to the problem of digitalis toxicity was the development

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* Prize Article. Awarded "GOLD MEDAL" for this paper.

* Paper read at the 12th Madras State Medical Conference, Coimbatore.

of the purified glycosides. These purified products were dissipated rapidly from the body so that even if toxic symptoms were to develop, they would subside promptly after discontinuing the drug. Digoxin and the preparation lanatoside Cobtained from Digitalis lanata came up to the expectations, but digitoxin did not. The problem of toxicity developing, however remained. The ideal preparation would have been one that was less inclined to produce toxic effects. The therapeutic range for the three glycosides, digitoxin, digoxin, and lanatoside C and for digitalis leaf were similar. Gitalin offered some hope in this direction.

Gitalin was first isolated from Digitalis purpurea by Kraft in 1912, and was believed in the continent, where it was known as verodigen, to be superior to the other digitalis glycosides[4]. Gitalin was studied by American workers and their earlier reports lacked much enthusiasm and it was not accepted as standard therapy. Interest in gitalin was reawakened following the reports of Batterman et al, who demonstrated its stability and uniformity. [1,2]

Gitalin as obtained from Digitalis purpurea is an amorphous, white powder. It is known as gitaligin in the U. S. A. Haring and Luisada found that the digitalizing dose of gitalin by the intravenous route is the same as by the oral route, indicating a relatively complete absorption from the alimentary tract [6]. Rate of dissipation from the body is intermediate between the rapidly eliminated digoxin and the slowly eliminated digitoxin [1]. It was also found to be equally potent to the other digitalis glycosides in initiating and maintaining digitalization in patients. Its greatest virtue was its lowered toxicity.

CLINICAL EXPERIENCE

I have been using gitalin over the last year and a half in the management of congestive cardiac failure. I have been using it side by side with the other commonly employed digitalis preparation digoxin, to study the comparative effects of the two. Its value, as well as the value of digoxin was most appreciable in patients with atrial fibrillation. I shall outline my clinical experience with gitalin under the following heads :

Initial Digitalization : Gitalin proved to be a valuable drug in initiating digitalization, particularly by the rapid method. It was particularly valuable for the advanced case of congestive heart failure with massive cardiac enlargement, where the early appearance of toxic symptoms seem to be rather high. The criteria adopted for adequate digitalization were the following :

1. clinical improvement, such as relief of dyspnoea, lessening of oedema and diminution of hepatomegaly, and

2. a decrease in the heart rate to around 70 per minute. The latter was most useful in patients with atrial fibrillation, being less significant in those with normal sinus rhythm. The more accurate assessment of the ventricular rate by taking it after intravenous administration of atropine was not carried out.

In the instance of a child aged 10 years with a rheumatic mitral heart disease, massive cardiac enlargement and atrial fibrillation, digitalization could not be achieved with digoxin because of the appearance of toxic symptoms before any therapeutic effect appeared. Digitalization was achieved with gitalin without any toxic symptoms developing. The patient was put on 2 mgms., of gitalin every six hours. On this regime digitalization was reached in 24 hours, after consuming 8 mgms. of gitalin. Dimitroff et al observed that in 8 of their 68 patients, digitalis leaf, digoxin or digitoxin could not be given in effective doses because of the development of

toxic symptoms. With gitalin however, the cardiac status of all the patients improved and the toxicity disappeared[4].

In another case of a female patient with a mitral heart disease, massive left atrial enlargement and atrial fibrillation, digitalization was achieved with 3 mgms. of gitalin in 24 hours. In another patient with atrial fibrillation, a one-dose digitalization with gitalin was attempted. After a single dose of 3 mgms., of gitalin there was a pronounced clinical improvement and the cardiac rate had come down to 90 per minute in 8 hours.

In a case of chronic pulmonary heart disease due to emphysema, administration of gitalin 1 mgm., every 8 hours brought the clinical condition under control in about 3 days. In another case of congestive heart failure with sinus rhythm due to aortic disease, partial digitalization was achieved in 3 days on a dosage of 1 mgm. of gitalin thrice daily. One of my patients developed congestive cardiac failure 24 hours after an extensive anterior myocardial infarction. He was put on 0·5 mgm., of gitalin three times daily. Clinical improvement appeared after 6 days of therapy i. e., after 9 mgms., of gitalin.

As alluded to before, the clinical improvement was most marked in those with atrial fibrillation. In cases with normal sinus rhythm, the clinical improvement though present, was not so striking.

For digitalization it is essential to have an idea of average digitalization dose of the drug. For gitalin this has been found by various observers to be between 5·0 and 6·5 mgms.[1,4], and the range is between 3·0 and 10·5 mgms.[7] Weiss and Steigmann using a dosage of 1–4 mgms., 1–3 times daily controlled the symptoms cardiac failure in the average case after a total dose of 5·9 mgms. The individual digitalizing dose varied from 4·0 to 9·5 mgms., the time required for digitalization being anything from 1 to 5 days, with an average of 2–6 days. For one day digitalization five patients required 6 mgms., and one patient, 5 mgms.[9] In my series most patients were brought under control with 5 to 6 mgms., with a range varying from 3 to 8 mgms.

For digitalization by the rapid method, I use the following regime:

For an average adult I compute the total digitalizing dose to be approximately 5 mgms. I give half the digitalizing dose viz., 2·5 mgms., immediately followed by half of the remainder, viz., 1·25 to 1·5 mgms , 6 hours later, depending on the clinical condition. Thereafter I administer 0·5 to 1·0 mgm., every 6 hours till signs of digitalization or toxicity appear. Most of the patients do not require the third or the fourth dose. By this method digitalization can be achieved within 24 hours without any toxic symptoms developing. Using a similar schedule for digoxin, where I compute the digitalizing dose to be of the order of 3 mgms., similar clinical results appear but in a large number toxic symptoms develop. This method of rapid digitalization has been on more than one occasion life saving. Before the advent of gitalin I used to feel that the clinical improvement noticed in patients with severe congestive failure was so gratifying that the development of some toxic symptoms in a few was well worth the risk. With gitalin this risk is definitely less.

When digitalization was not an urgent need, I use the slow method employing 0·5 mgms., 3 to 4 times daily. Digitalization is achieved in 3 to 5 days time, sometimes more. When using the slow method allowance has to be made for the amount of digitalis eliminated or destroyed during the period taken for digitalization. Thus the amount

required for digitalization by the slow method is more than by the rapid method.

Maintenance: The dose required for maintenance of digitalization is the amount necessary to keep the patient symptom free and the ventricular rate at about 70 per minute. In most patients the maintenance dose was between 1 and 2 mgms., per day. The larger dose was more commonly needed in those with sinus rhythm. Persons with atrial fibrillation could be maintained on 0·5 mgm. per day. In my limited experience gitalin has not proved to be very valuable for maintenance therapy in a few cases. Some of the patients could not be maintained even on such high doses as 1 mgm., four times daily. Weiss and Steigmann found 0·5 mgm., daily to be both adequate and non-toxic.[9]

Toxicity : None of the patients so far treated by me have had any toxic symptoms. In one of my patients who was on a maintenance therapy with 1·5 mgms., of gitalin daily, there was an inadvertent doubling of the dose. Apart from a bradycardia there were no other undesirable effects. A similar observation, though deliberately perfomed was reported by Weiss and Steigmann [9]. In a series of 9 patients on maintenance therapy with gitalin, a doubling of the minimal therapeutic dose resulted in toxic symptoms appearing in two cases only. Of the remaining, two developed toxic symtoms when the dose was increased three times and the rest did not exhibit any even on increasing the dose three to six times. They observed that subjective symptoms of toxicity developed in only three of their nine patients who developed toxicity with gitalin. The remaining had only electrocardiographic evidences of toxicity. They suggest that patients on gitalin therapy should be very closely watched for arrhythmias.

Dimitroff et al remarked that improvement was so remarkable in each and every case that there was no deliberate or inadvertant instance of toxicity in their series.[4]

Batterman et al found that the therapeutic ratio, i.e., the ratio between the digitalizing dose and the toxic dose, was approximately 60% for the commonly employed digitalis preparations (digitalis leaf, digoxin and digitoxin.) With gitalin however, the therapeutic ratio was 37%, in other words, the average digitalizing dose is about 1/3rd the average toxic dose [1]. In their experience the average therapeutic dose was 5·7 mgms,, and the average toxic dose was 14·1 mgms.

Weiss and Steigmann reported in their series of 49 cases, a therapeutic ratio of 42%. Thus most of the available reports stress on the high therapeutic ratio of gitalin. There is one recent publication by Bryfogle et al who by using methods somewhat different from those employed by previous workers studying gitalin, failed to support the results of the other observers indicating a wider therapeutic range with gitalin [3].

Comparison with Digoxin : For initial digitalization both gitalin and digoxin compare favourably. There is a selected group of patients, where gitalin seems to be particularly useful. Persons with advanced cardiac failure have been noted to tolerate digitalis preparations poorly. They develop toxic symptoms even before any therapeutic benefit is noticeable. A case belonging to this group has been referred to earlier. It is in this group that gitalin is very useful.

In my study, patients who had been initially digitalized with digoxin and were on maintenance therapy with it were transferred to gitalin and vice versa to study the equivalent dosage of the two preparations. It was found that 0·25 mgm., of digoxin was equivalent to 0·5 to 0·75 mgm., of gitalin. In some the equivalent dose was 1 mgm., of gitalin.

In the series of 68 patients reported by Dimitroff et al, 45 had been digitalized and satisfactorily maintained on other digitalis preparations. 85% of these patients could be maintained satisfactorily on 0·5 mgm., of gitalin, while the rest required larger doses.

With regard to the development of toxic symptoms gitalin compared very favourably with digoxin. On the rapid one-day digitalization programme, quite a few of the patients on digoxin developed toxic symptoms, whereas none of those controlled with gitalin developed it.

CONCLUSION

As a result of intensive studies it can be said that as far as therapeutic benefit is concerned, gitalin can compare favourably with any other digitalis preparation. Its superiority over them is in the low incidence of toxic symptoms.

The problem of toxic symptoms developing after exhibition of any digitalis preparation is a complex one depending on factors more than those inherent in the drug itself. With the advent of the purified glycosides, digoxin, lanatoside C and digitoxin, the incidence of toxicity was expected to decrease. On the contrary, there are reports on the mounting incidence of digitalis intoxication.

One factor is the increasing use of the rapid method of digitalization, particularly by the parenteral route and to the use of the one-dose method based on the dogmatic statements on the total digitalizing dose. This risk was particularly noted with digitoxin. Individuals vary with regard to the amount of drug required for digitalization. It is for this factor of variability I advocate the use of half the calculated digitalizing dose for initiating digitalization. By this technique the chances of patients developing toxic symptoms is reduced to the minimum.

Another factor that may be responsible for the greater incidence of toxicity, is that some of the patients in this era of antibiotics live longer and this renders them likely to have grave cardiac damage. Such badly damaged hearts are more liable to the toxic effects of digitalis preparations. Such a situation also occurs in the younger patients with cardiac lesions producing gross cardiac enlargement and pronounced symptoms.

A more important reason may be the electrolyte disturbances that so regularly accompany the enthusiastic desalting procedures employed in the management of cardiac failure. These electrolyte abnormalities, particularly that of potassium depletion seems to lower the threshold of the already damaged myocardium for the development of digitoxi-city.

Thus we see that the problem of digitalis toxicity is multifaceted. The intrinsic character of the drug is but a brick, albeit a significant one, in the whole structure. Gitalin is one drug that may prove to be the digitalizing agent with this character of low toxicity inherent in it. Though many may not agree with the statement of Batterman et al, that, " on the basis of therapeutic range, dissipation, uniformity from lot to lot, constancy in absorption, gitalin (amorphous) is the digitalis preparation of choice for the usual patient with congestive heart failure ", the wealth of evidence seems to be in favour of it.

The observation initiated by the English physician and botanist, William Withering in his ' Account of the Foxglove and some of its Medical Uses ", published in 1785 after ten years of intensive studies may one day lead to the development of a preparation bereft of all toxicity–a Utopia in medical practice.

Acknowledgment: The gitalin used in this study was made available through the courtesy of Mr. Amrut V. Mody of the Unichem Laboratories, Bombay. Thanks are due to him for liberal supplies of the drug.

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SUBARACHNOID HAEMORRHAGE*

by

Dr. B. RAMAMURTHI, M.S., F.R.C.S., MADRAS.

I am grateful for the opportunity given to me by the Indian Medical Association to present this paper on Subarachnoid haemorrhage as I want to put before you certain aspects of the subject that is engaging the attention of the Neurologists and Neurosurgeons all the world over for the past one decade. Subarachnoid haemorrhage has been recognised only for the past seventy or eighty years. Before that it was confused with intra-cerebral haemorrhage which is commonly known as cerebral apoplexy. Haemorrhage into the subarachnoid space is caused by a blood vessel rupturing into the subarachnoid space. This is usually due to a small aneurysm in the blood vessel in the younger group of patients. In the older age group it may also be due to congenital aneurysm but the feature of arteriosclerosis also comes into the picture. Small aneurysms are due to congenital weakness in the medial muscular wall of the cerebral blood vessel leading to a protrusion of the wall of the blood vessel. This may go on throughout life without endangering the life of the person.

But sometimes due to various known and unknown reasons this aneurysm may suddenly rupture. Once it ruptures the progress of the case depends upon the size of the aneurysm and its site. When a big aneurysm ruptures and there is an enormous quantity of blood thrown into the subarachnoid space it may end fatally. Sometimes the aneurysms may rupture partly into the subarachnoid space and partly into the brain. When the blood leaks into the brain it forms an intra cerebral haematoma and may cause severe fatal pressure on the brain. Occasionally this haematoma may also burst into the ventricle causing fatal intra ventricular bleeding. Very often it so happens that the bleeding occurs slowly into the subarachnoid space.

When the aneurysm begins to bleed, symptoms are caused by the presence of blood in the subarachnoid space. This is chiefly manifested by the occurrence of a very severe headache. Usually the onset of the headache is very sudden. The patient may loose consciousness for a few minutes or for a long time. Loss of consciousness depends upon the size of the bleed. Headache persists and may spread from the temporal region of the frontal region to the back of the neck and also along the spine to the lumbar region. This headache and pain in the neck and the back is due to the presence of blood irritating the meningies. The headache may persist for a few hours or more likely for a few days. In addition to the presence of pain and headache the patient may exhibit occasionally other neurological signs that may give a clue to the side of the subarachnoid haemorrhage. There may be a third nerve paralysis or disturbance of vision on one side. There may also be presence of weakness of one limb or the other. Occasionally an aneurysm may manifest itself solely by a focal neurological lesion when the leak is minimal.

Diagnosis. Diagnosis of a subarachnoid haemorrhage is chiefly made from the history of the case and is confirmed by lumbar puncture. In any case of sudden severe headache (occurring almost like a bolt from the blue) lumbar puncture is an essential procedure. Lumbar puncture

* Paper delivered at the annual conference of Madras State Branch of the Indian Medical Association in November 1957, at Coimbatore.

reveals blood uniformly mixed with the cerebrospinal fluid. If the lumbar puncture is done later within the 24 to 48 hours then actual blood may not be seen in the blood but the cerebrospinal fluid may be coloured yellow and may have a very high protein content.

At this juncture, I want to stress one fact-namely the *Rarity with which Subarachnoid Haemorrhage has been diagnosed in this part of our Country.* In the General Hospital records there are only a few cases of subarachnoid haemorrhage. This may be due to the rarity of subarachnoid haemorrhage among us but probably is more likely due to our not diagnosing this condition. This matter is worth your attention specially because a definite diagnosis of the type of aneurysm is possible by modern methods and curative surgical treatment can be adopted.

When the case is diagnosed as a subarachnoid haemorrhage further treatment has to be decided. If the patient is acutely ill only conservative measures are to be adopted for the first 24 to 48 hours.

Cerebral angiography is absolutely essential in every case of subarachnoid haemorrhage. I prefer to wait at least two or three days after the onset of haemorrhage before advising cerebral angiogram. Most of the Neurosurgical Centres in the world follow a similar programme though there are certain differences of opinion. The need for cerebral angiography is to diagnose the site of the haemorrhage so that further definitive surgical treatment may be decided upon. Cerebral angiography is done on both sides. If there are any focal neurological signs the angiogram is done on the corresponding side. If on finishing the angiogram on one side no aneurysm is visualised then the other carotid angiogram is done. If bilateral carotid angiography does not show any aneurysm, it may be necessary to do a vertebral angiogram. After this investigation is completed treatment is decided depending upon the site of the aneurysm.

Without going into elaborate details of treatment, I would just point out here that in any aneurysm of the internal carotid artery upto its bifurcation, carotid ligation in the neck may suffice to give a good chance for the aneurysm to heal. On the other hand aneurysms of the circle of Willis require a direct intracranial attack. The results of the surgical treatment have been followed up very carefully by many centres and it has been found that surgical treatment definitely offers a better chance of a complete cure than the conservative treatment. To put in a nutshell the experience regarding prognosis that has accumulated during the past few years all the world over I would say :

(1) when complete cerebral angiography does not reveal the presence of any aneurysm it is found that the prognosis is much better with conservative therapy than conservative therapy in cases in which a definite aneurysm is demonstrated.

(2) The result of the conservative treatment have shown that if a patient escapes the recurrent bleed within the first eight weeks, the chance of further bleed is slightly less. But within the first eight weeks the chance of a recurrent haemorrhage are indeed great. About onefifth of the cases of subarachnoid haemorrhage go through life without much further trouble. The rest (80 percent) of these cases run a grave risk of a sudden fatal haemorrhage. In such circumstances surgery has come as a definite life saving measure.

One other aspect I would like to stress is the advances that have been made in

the surgical treatment. After opening the skull and reaching the site of the aneurysm the aneurysm is carefully dissected from the surrounding tissue and is clipped.. If complete isolation is not possible it may be partially clipped and muscle wrapped around it. If the artery is not a main one the aneurysm is isolated by clipping the artery proximally and distally. During the dissection of the aneurysm, the aneurysm may rupture. It may be necessary at this stage to occlude the parent vessel. In such circumstances the risk of lack of blood supply to the brain occurs and a permanent neurological deficit may be precipitated. But this has been avoided by operating under hypothermia. The patient's temperature is brought down from the normal (about 36°) centigrade to 27° centigrade. At this temperature the brain is able to withstand the anoxia for a much longer time and this facilitates the surgeon to isolate the vessels and the aneurysm calmly and without any hurry and then clip its neck. Thus in our experience hypothermia has been a boon not only in the treatment of aneurysms but also in the treatment of advanced intracranial tumours. The Neuro-surgeon has got much to be thankful for his colleagues, the radiologist for accurate diagnosis and the anaesthetist for facilitating accurate surgery.

Ladies and gentlemen—thus you see that surgery has taken one more stride in alleviating human suffering by better treatment of some of the dire consequences of subarachnoid haemorrhage. Hence it is my earnest plea that we pay more attention to these cases of subarachnoid haemorrhage as they commonly occur in the younger people who are otherwise healthy. If the aneurysm is dealt with they can lead a normal life.

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RECENT ADVANCES IN SURGERY*

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By

Dr. R. Gopalan, B.A., M.B.B.S., *Tirunelveli.*

It is with great trepidation that I rise (this evening) to discuss with you on some of the aspects in which Surgery has progressed during recent years. Fully conscious of the utter incompetency on my part to deal with such a vast subject in such a short time and painfully aware of my shortcomings, I had the temerity and rashness to choose this subject as I was confident that even if I discussed on some remote aspect of medicine which has advanced during recent years, I can very well justify the title of my subject, for, the recent advances in Surgery are not merely the advances which surgery per se has made but also the impact which advances in all branches of medicine have made on surgery making the hazards of surgery less than the hazards of daily life.

The advances which surgery has made during recent years are tremendous. Regions of the body which were considered as quite inaccessible, are approached, organs which were considered as untouchable are attacked and procedures which were considered as lethal are performed almost daily with impunity in almost all the major surgical clinics in the world.

Today, Surgeons in England have attempted hypo - physectomy, bilateral adrenalectomy and oopherectomy for advanced cancer of the breast with visceral metastases where the primary has already been removed by a radical mastectomy and have given short-term reports about the encouraging results of such breath-taking operations—I mean our breaths—not those of the patients. Pelvic eventration for genital cancer in women with pelvic metastases has become the accepted method of treatment in such cases as to be mentioned as an innovation.

Thoracic surgery and cardio-vascular surgery have both progressed much during the past decade or two. Surgery has made inroads in the treatment of tuberculosis so that resection is an accepted method of treatment in selected cases of pulmonary tuberculosis. Pneumonectomy, exploration of the mediastinum, intra cardiac operations—all these can only be imagined by many of us as possible. A decade or two ago, if a medical student who has reached what he hopes to be his final year, is asked the treatment of an aortic aneurysm and he blurts out inadvertantly of resection, his hope is blasted. But today with the progress of surgery, resection of an aortic aneurysm is done with restitution of the resected part with a natural aortic graft or a synthetic plastic tube and is the method of treatment in such cases.

Intracranial operations like ablations of portions of the brain and leucotomies for psychiatric conditions, operations on the sympathetic system like total sympathectomy for malignant hypertension, one stage abdomino-perineal resection of the colon for malignant disease of the rectum and many other procedures ridiculed at one time as carnivorous surgery have by their long term results found a place in the management of the appropriate condition.

These hazardous procedures have been made quite safe and routine not only

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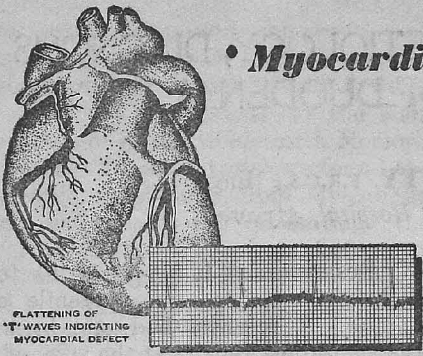
* Paper read at the 12th Madras State Medical Conference, Coimbatore.

because of the technical advances in the field of surgery but also because of the tremendous and rapid advances which medicine has made in other branches especially in the field of anaesthesiology, pharmacology, biochemistry and knowledge of the body fluids and the electrolyte balance. Anaesthesia has progressed to such a high level of perfection that no one need die because of anaesthesia and the choice of anaesthetics is so numerous and varied as to suit even the most fastidious or the poor risk cases. During operation the patient is put into a state of hibernation - cold and bloodless by the use of appropriate drugs as the lytic cock tails - which produce hypothermia and hypotension. In fact, anaesthetists, today, are blamed of making a hair - splitting difference between life and death. Insensitive to pain and external stimuli, cold and pulseless, with the respiration under control and not voluntary, it is really difficult to say whether the patient is alive or dead - living or dying. Our knowledge of biochemistry has advanced to such an extent that a correct estimation of the fluid and electrolyte requirements of the patient before, during and after operation, is made every day and no patient is lost either due to dehydration, overhydration or fluid and electrolyte imbalance. The correct indication and the proper time for administration of blood and plasma and their substitutes are now well-understood so that blood transfusion has made possible the undertaking of major surgery like pneumonectomy and intra cardiac operations.

Thus surgery has advanced by leaps and bounds during recent years and is still advancing. Much of the advance has been due to the improved techniques in operation and more of it due to a better understanding of the human body during health and disease and the special requirements necessary to adjust the human mechanism - before, during and after an operation. Recent advances in the field of anaesthesiology, biochemistry and physiology have contributed not a little to the safety and progress of the patient undergoing a major surgical manoeuvre. Thus today surgery is safe. Perhaps in America there are more deaths today on the road than on the table.

All this and much more about the gratifying results of surgery and its safety is all good but let us not be carried away by this. It is now more important than ever before, to see, that before we subject anybody to surgery that there is an adequate indication for surgical interference ; for, after all when all is said and done, surgery, however safe it may be, is in most cases an interference though in many cases it may be life - saving. The selection of patient, the time of operation, the choice of operative technique and the adequate care of the patient throughout - all these raise surgery from a Science into an art. In the words of Lord Moyinham–"Surgery has been made safe for the patient ; it is for us to see that the patient is made safe for surgery." Today, when surgery is safe, the temptation to do surgery for surgery's sake, to call in surgery as an aid to even diagnosis is really great. To open up and see is alright as a dictum to be followed when all methods of diagnosis are explored and the surgeon is at his wit's end to find out the trouble but to adopt it as a policy to avoid the inevitable doubts and delays in diagnostic methods is, to say the least, inexcusable. Let us know our limitations, let us know when to operate, but more than that let us know when not to operate. In the inimitable words of Sir Robert Hutchison " From inability to let well alone ; from too much zeal for the new and contempt for what is old ; from putting knowledge before wisdom, Science before art and cleverness before common sense ; from treating patients as cases and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us."



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OBSERVATIONS ON THE ETIOLOGY, DIAGNOSIS * AND MANAGEMENT OF DUODENAL ULCER

by

DR. FRANK I. TOVEY. F.R.C.S., (Eng.)

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THE incidence of duodenal ulcer seems to be rising throughout the whole world. In the West it has been associated with the increased tempo of living, but in the East this does not seem to be the true explanation. We in South India are living in an area where duodenal ulcer is common. It seems to exist especially in pockets, there is a high frequency in and around Mysore and we know that it is common in parts of Madras and in Travancore. Fundamentally there is nothing to distinguish a duodenal ulcer that occurs in the East from that which occurs in the West, but I think most surgeons would agree that in the West they have never seen such large, hard, callous ulcers as we see here in the East. The amount of scarring and fibrosis is at times truly amazing and sometimes the ulcer' forms a mass that is almost tumour-like in its consistency. In the West also the ratio of duodenal ulcer in men to duodenal ulcer in women tends to vary from country to country. In some countries it is only 2 to 1, but in England and America it is mostly 9 to 1. As far as we can tell from our small figures in Mysore the ratio of men to women in India is even higher and must be something like 10–15 to 1. We find that the women patients very rarely come in the acute stage and usually come very late when they have established pyloric stenosis. For the most part their symptoms of the ulcer have been very mild and have not been enough to bring them to hospital.

Most of the cases fall in the age group 20 to 30, but we do get a definite number of cases occurring in people of 40 to 50 and, from time to time, juvenile cases appear. I recently had one in whom the symptoms started at the age of 12, and another in whom the symptoms started at the age of 14

Sir Heneage Ogilvie has said about the West — "only the best chaps get duodenal ulcer". By this he meant that it was the conscientious, hard working man who is the one who is most likely to get duodenal ulcer. I think perhaps he had doctors in mind, people who work long hours, who tend to worry about their work, who are thorough and conscientious in all they do, and I think this very aptly describes the duodenal ulcer patients seen in the West. I am not saying that duodenal ulcer patients in the East are not conscientious in their work, but they do fall into a different class. For the most part it is the poor man, the ryot, the unintelligent and the uneducated man who gets the duodenal ulcer. The reason for this is not fully understood and various theories have been suggested. Howard Somervell thinks it is due to a poor quality diet, low in vitamin B; and spiced highly to make it palatable. This is very true of our cases in Mysore and of his cases in Neyoor. I believe it is true that duodenal ulcer is very rare in the Punjab where the diet is quite different and the consumption of milk is much higher.

When I first came to Mysore in 1951 I wondered whether there was any

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* Address delivered at the meeting of the Nilgiri's Branch held on 17—5—57.

association between hookworm infestation and the high incidence of duodenal ulcer there. From 1952 to 1954 we did a survey of admissions to the Men's Department of the Holdsworth Memorial Hospital. To our surprise we found that over 40% of patients from Mysore City itself had hookworm infestation, that 70% of the patients from Coorg, and 95% of the patients from the Biligiris had hookworm infestation. In a series of 986 patients reviewed from 1952 to 1954, 388 had hookworm infestation, about 34%. About 20% of these cases came with symptoms of duodenitis, that is to say epigastric hunger pain relieved by food and alkalies, and I wondered whether there was any association between this and duodenal ulcer. Of the 388 cases with hookworm infestation 43 had duodenal ulcer, i e. 11%. Of the 986 cases reviewed 106 had duodenal ulcer, again approximately 11%. Also, in the 106 cases of duodenal ulcer 43 had hookworm infestation which makes approximately 40%, which is not statistically different from 34% over the whole series of cases reviewed. In this way I think we can establish that there is no causal relationship between hookworm infestation and duodenal ulcer, but it is interesting to note that of the 388 cases with hookworm infestation about 20% could have been diagnosed as duodenal ulcer if careful Barium Meal and stool investigations had not been carried out.

The symptomatology of duodenal ulcer can be most variable. Classically, of course, it is right epigastric pain which is felt when the patient is hungry and at night, and is relieved by food , but very often it does not follow this pattern. Sometimes the patient feels a pain in the left hypocondrium, sometimes even below the left scapula , at times the pain is felt down in the left iliac fossa, (when I venture to think that it may be due to associated spasm of the colon) The most typical thing about the pain however, is its periodicity, though this is by no means invariable. When a patient says that he gets pain which comes for three or four weeks and then goes for two or three weeks and then comes back again it is a very suggestive feature and I think also that pain which wakes a patient up in the early hours of the morning is quite characteristic. Local tenderness is by no means always found, but when it is present it is a very valuable help. The tenderness in hookworm duodenitis is less well localised and quite often can also be felt to the left of the midline in the epigastrium over the duodeno - jejunal flexure. A Fractional Test Meal is still much in vogue, but more and more people cast doubt on its usefulness. I myself, very rarely have it done. From the experiments on Alexis St. Martin we all know how much the acidity may vary in the course of a single day and how much it depends on the position of the gastric tube and on the amount of duodenal regurgitation. It is of occasional value in picking up cases of achlorhydric dyspepsia and also in the diagnosis of gastric cancer. Here again the presence of acid does not exclude gastric cancer but the presence of blood in any significant amount should put one on the lookout.

When deciding whether a patient is suitable for Gastro-enterostomy alone it is helpful to have an estimation of the night acid secretion which is dependent on the vagus. If the volume of the night acid is over 500 cc's, or, if the free acid exceeds 45 units, and the total acid 65 units, it means that there is a high risk of Stomal ulceration if a Gastro-enterostomy is done alone. The keystone of diagnosis still lies in a Barium Meal, but this is beset also with difficulties. In hookworm duodenitis one gets a tender duodenal cap which remains in spasm, relaxing only now and again to fill completely , this may be easily mistaken for a duodenal ulcer and it is important

to try and demonstrate an actual ulcer crater. In cases of post-bulbar ulcer, that is to say, an ulcer at the junction of the first and second part of the duodenum, one sees a normal duodenal cap and the demonstration of the ulcer crater can be extremely difficult indeed.

Before we go on to the question of treatment it is important to consider the mechanism of acid secretion in the stomach. This is under dual control. First of all, there is the hormonal secretion which is under the control of gastrin which is secreted by the mucosa of the pyloric end of the stomach in response to direct stimulation by the presence of food. There is also entro-gastrone which is secreted by the small intestines and inhibits the secretion of acid. Secondly, there is the nervous secretion which is under the control of the vagus and which is brought about by the sight of food etc. It is this secretion which is thought to be largely responsible for the production of duodenal ulcer. It is greatly increased in a patient who is in a state of anxiety or tension and it reaches especially high levels at night in patients with duodenal ulcer. Any treatment must be designed at dealing with both types of secretion. In any given case one has to weigh between the merits of medical treatment and surgical treatment. Let us first consider medical treatment—we all know that a superficial ulcer of the skin will heal readily in a matter of two weeks or so, but this does not apply to an ulcer in the intestinal canal subject to the irritation and passage of acid and food and it is probable that a period of at least four or six weeks is required for its healing. During this period it is very important that the patient should be at rest and very often for the patient to obtain adequate rest this is synonymous with admission to hospital. It is not important only that the body should be at rest, but the stomach should be at rest too, and this is obtained by frequent feeding. The patient should put something into his stomach at least every two hours. This frequent feeding is really more important than the type of food that the patient takes. As long as he avoids coarse food and spices and chilies I do not think it matters very much what type of food he takes for his main meals. In between, there is little doubt that milk is the food of choice. Milk has an excellent buffering action and I like to give my patients 4 ozs. of milk two hourly in between their main meals. I have found that skimmed milk on the whole gives just as good results as full cream milk. Full cream milk has the advantage that the fat present delays the stomach emptying, but this effect can be obtained by giving the patient olive oil, or arachis oil in place of the cream of the milk. The buffering action of the milk is unaffected by the absence of its fat content. Patients who cannot afford full cream milk can often manage to obtain adequate supplies of the skimmed milk. To reduce vagal secretion sedation with Luminal by day, Grs. ½ t.d.s., & Medinal Grs. 10 at night is helpful ; combined with the judicious use of antispasmodics. Many antispasmodics are on the market and they all have their peculiar advantages. For a busy business man who is having a period of worry I think there is probably nothing better than a drug such as Probanthine, or Antrenyl. But for the average man Tincture of Bellodonna is quite satisfactory and can be added to the alkaline mixture which it is our custom to give. There are also many alkaline mixtures on the market and they all have various advantages, but in ordinary hospital practice I think a mixture of equal parts of Magnesium Carbonate Levis and Calcium Carbonate one drachm of each to ½ oz. of Aqua Chloroform is quite satifactory. If the patient is constipated the amount of Mag. Carb. Levis can be increased and if he has a tendency to diarrhoea the amount of Calcium Carbonate can be increased. If desired Kaolin can be added to this mixture. It is my custom to give ½ oz.

of this mixture two hourly to acute cases, and ½ oz. after food to convalescent and chronic cases. To it I add 10 to 15 minims of Tincture Belladonna to each ½ oz. This means that an acute case is getting this dose of Belladonna every two hours and I do not find that it causes any symptoms of overdosage. In addition to the above medical treatment we forbid our patients to smoke and also to take alcohol. In between the attacks patients have to be advised to avoid long intervals of between meals and on the first sign of return of symptoms to go back to bed and to take two hourly feeds of milk and two hourly doses of alkalies.

When one considers all that medical treatment means with regular periods of rest, expensive treatment with alkalies and milk, (if these have to be purchased at home), it is small wonder that the average duodenal ulcer patient in South India, who is a ryot, can rarely afford to stick to such a course. For this reason many of us think that the treatment of election in the poorer type of patient is to offer surgery right from the beginning if his symptoms have been of any duration. The question often is, what type of surgery is best for these cases ? Gastroenterostomy is a well tried and well proved operation and I still think it is the best and safest operation for small hospitals. However, there is a very definite incidence of anaetomotic ulcer but it is difficult to get accurate figures for this in South India. I think it is the experience of most surgeons however that such cases occur quite regularly. Western figures give the incidence of anastomotic ulcer as being from 5 to 15% according to the series and my own feeling is that the frequency is just as high here in South India. Because of this I think that whenever facilities are available Gastrectomy is probably the better operation to offer the patient. Gastroenterostomy can be reserved for patients with pyloric stenosis over the age of 40 who have a low night acid; or, in patients who are not fit for the bigger operation of Gastrectomy it can be combined with Vagotomy if their night acid is of a high level. It would be out of place in a lecture like this to go at any length into details about the various techniques of Gastrectomy. There are two points, however, which I would like to mention.

The first point I should like to mention is the difficulty of duodenal disection in many of the ulcer cases which I see. As I have said before the ulcer often forms a hard, callus-like tumour mass, for this reason I think it is often best to set out right from the beginning to aim at doing a pre-pyloric closure. The mucosa of the pyloric antrum is cored out and a closure is obtained by sewing the sero-muscular wall. This procedure is greatly facilitated by infiltration with saline and 1/200,000 Adrenaline into the space between the muscle layers and mucosa. The second point I wish to make is about the size of the stomach remnant. At first I was greatly concerned lest patients who had had a Partial Gastrectomy would suffer greatly by the inability to take one or two large rice meals per day, which is the custom of the people here. I must say that I often wondered how a normal person was able to get so much rice into his stomach in so short a time and I felt that a person with a small stomach such as that left after Partial Gastrectomy would be under a great handicap. I studied this problem for some time and I found that the capacity of food after a Partial Gastrectomy did not seem to depend very much on the amount of stomach which was left behind or on any valve formation or on the size of the stomach. It seemed to depend much more on the ability of the jejunum to take up the food, and this seemed to vary in different individuals. Most cases, however, after an initial period of six or nine months found that

they were able to take adequate amounts of food. I am not sure, however, whether the general nutrition of patients with a large stomach remnant is not better, and I am still wondering if there is a case for doing low Gastrectomies and combining them with Vagotomies with this end in view. It is too early to make a definite statement about this and cases will have to be followed up for a much longer time.

I do not want to spend much time dealing with the complications of duodenal ulcer These fall into two groups. Firstly, the complications of surgery which includes a 'dumping syndrome' after Partial Gastrectomy, and anastomotic ulcer which can occur after either Gastrectomy or Gastro-enterostomy, but is much more common after Gastroenterostomy. There is a definite place for the use of Vagotomy in the treatment of anastomotic ulcers which are not complicated by fistula or scarring. I have been surprised at the number of cases with anastomotic ulcer after Gastroenterostomy which have a silent gastro-jejunal colic fistula. This has often been only found by noticing a strange smell about the stomach wash-out. Radiologically it is best demonstrated by doing a Barium Enema which will show barium flowing through the fistula into the stomach and jejunum. With regards to complications of the ulcer itself, apart from pyloric stenosis, perforation and haemorrhage are the main problems. While the conservative treatment of perforation is still to be recommended under difficult circumstances, such as on a ship at sea, it is still generally agreed that whenever possible surgery is the best means of dealing with a case. In the treatment of haemorrhage, the difficult decision is always when, and in which case, to operate. It is propably a wise decision to attempt surgery in a young man in which the haemorrhage is severe and continued especially if he gives a history of previous bleeds, and it certainly should be considered in all men over 40 who have a second haemorrhage or a haemorrhage that is continuing for more than 24 or 36 hours.

Before closing there is one matter which I should like to bring to your attention in the management of pyloric stenosis. These cases need very careful preparation for surgery and it is not very well known that the vomiting is often not due so much to the pyloric stenosis as due to salt depletion which in itself is a cause of nausea and vomiting. Many of these cases settle down quite well with a regime of stomach washouts with salt replacement through the tube by mouth and parenterally. This will often give one a few days grace to make a very sick patient fit for surgery. One must not forget also that these patients often have severe potassium depletion which has to be borne in mind.

Much work needs to be done on this question of duodenal ulcer ; its etiology still remains a mystery ; Partial Gastrectomy while offering the best means of obtaining total cure still presents many problems. I think progress can only be made by those interested getting together and sharing their ideas. I often wish that we could have a society of Gastro-enterologists in South India.

INTESTINAL VIRUSES *

by

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It was demonstrated that poliomyelitis virus does multiply and produce cytopathogenic effect in cultures of non-neural tissues in 1949. This has added a valuable tool for the study of viruses. Work in connection with poliomyelitis and other viruses has considerably expanded the scope of application of tissue culture methods to virology. The antibiotics and chemotherapeutic agents have helped the control and cure of bacterial infections and focussed the attention of clinicians and virologists on viral diseases. The advances in tissue culture are in no small measure due to the antibiotics. They have greatly facilitated diagnostic work in viral diseases by the ease with which bacterial contamination could be controlled and viral isolations obtained from materials like throat swab, faeces etc.

In recent times a large number of viruses have been isolated from a variety of human and extra-human sources and the task of identifying them calls for a systematic approach and a good deal of work. As such a grouping of viruses based on the site of excretion in infected humans is a valuable starting ground before final labelling is undertaken from the virus workers' point of view. For a busy clinican grouping of cases of suspected viral aetiology based on specimen required for viral isolation may be more appeaeing especially when confronted with a group of more or less clinically similar cases.

Intestinal viruses are met with in good concentration in the faeces of infected humans. They can be isolated from the oropharyngeal region during the first few days of illness and from the faeces for a considerable period of time. Influenza and adeno-viruses, virus of infantile croup etc. though isolated from the oropharynx are not referred to as intestinal viruses. Further, some adenoviruses and the virus of herpes etc., may occur both in the nasopharynx and in the intestinal tract of patients, but are not classified as intestinal viruses.

Poliomyelitis, Coxsackie and *ECHO* (Enteric Cytopathogenic Human Orphan) viruses, virus of febrile exanthem, virus isolated from cases of epidemic exanthem associated with meningitis and perhaps some more viruses as yet unidentified may be referred to as intestinal viruses (e.g. virus of infectious hepatitis etc.).

Poliomyelitis, as a disease was recognised in the 18th century and systematic description of it was available during the 19th century. The susceptibility of the monkey to the infection was demonstrated only 50 years ago. The rodent pathogenic strains of polio virus were isolated about 20 years ago. Three types of polio virus have so far been met with.

Coxsackie viruses were first isolated in 1948 and are classified into group A and B based on the lesions produced by the strains in suckling mice. Antigenically it consists of 24 different strains, five of which are type B and the rest are type A. All strains are pathogenic for suckling mice while all the B group strains and two of the A group strains produce cytopathogenic changes in tissue culture also.

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* Lecture delivered at a meeting of the Nilgiris Branch on 27—7—57.

Enteric Cytopathogenic Human Orphan viruses had been recognised since 1949, when tissue culture methods came into extensive use. More than 14 serological types have been identified so far. The other viruses have been isolated only more recently. Most of these viruses have a size of about 10 to 30 mu as determined by ultrafiltration, sedimentation and electron microscopic studies. They resist the action of either in 50% concentration for periods over 2 hours at room temperature and withstand storage at - 20° C for prolonged periods. They are comparatively stable agents as regards storage and transport at temperatures above - 20° C.

Pathogenicity of these agents to laboratory animals is very limited. The polio viruses are pathogenic only to primates. Suckling mice preferably 24—48 hours old are the animals most susceptible to Coxsackie infections. The others are not pathogenic to any of the laboratory animals.

These agents produce an easily detected cytopathogenic effect in cultures of primate cells. Their pathogenicity to humans is well established by the demonstration of neutralizing antibodies in human gamma globulin and a significant rise in neutralizing antibody content in convalescent serum of patients. Complement fixing antibodies have been demonstrated in humans following infection with some of these agents but a reliable complement fixation test for routine use is yet to be evolved.

Clinical features: The diseases due to these agents occur mainly in summer months and commonly in epidemic form. Inapparent infections are common features of these agents. All age groups are susceptible to these infections but cases in children are more frequent. The clinical manifestations are of acute onset characterised by fever of varying degree and associated generally with oropharyngeal and gastrointestinal symptoms.

Meningitis of varying severity is also a feature. It is manifested by clinical signs and a variable increase in the cell count and protein content of the cerebrospinal fluid. These cases are usually referred to as aseptic meningitis or nonparalytic poliomyelitis, when poliomyelitis is present in epidemic form. Occasionally, an aetiological agent, not poliomyelitis virus has been isolated from the cerebrospinal fluid thus rendering spinal tap a valuable diagnostic procedure. The clinical features of illness caused by these viruses are described in tables I to IV.

Clinical course: All these infections except poliomyelitis run a short course with no mortality and varying morbidity rates. The febrile stage rarely lasts over 3 to 4 days. The duration of illness is 6 to 7 days at the most and is followed by a smooth convalescence. Paralysis and paresis of muscles are uncommon. It may be advisable to do a complete neurological examination at the onset of the disease, early in convalescence and 6 months thereafter, to exclude the possibility of central nervous system involvement.

Poliomyelitis: Abortive or minor illness and nonparalytic poliomyelitis follow the same course outlined above especially in tropical countries. The possibility that paralytic manifestations may follow these symptoms within a period of 3 to 15 days should always be borne in mind. Cases either suspected to be poliomyelitis or giving a definite history of contact with a case of poliomyelitis should be observed preferably at bed rest for a period of two weeks. This is essential as exertion at this stage is a predisposing cause to the onset of severe paralysis. The course of paralytic poliomyelitis is determined by the extent and degree of neuronal damage, resulting from viral action on the neurons.

Epidemiology: The seasonal incidence and epidemic manifestations have already

been referred to. The infections seem to occur all over the world. Epidemiological studies supported by laboratory data have indicated that only one agent of this group is responsible for the epidemic at any one time. The viruses are serologically distinct and hence the same patient may have repeated illnesess due to infection by a different virus. The mode of spread of these agents is not well understood but is considered to be by the oropharyngeal and intestinal routes as in the case of poliomyelitis. Virus is excreted in the faeces for fairly long periods following infection which may be sub-clinical and this is responsible for the epidemic prevalence of the disease. Attempts to incriminate strain difference in the viruses for causation of epidemics have not so far been successful.

Diagnosis: The diagnosis of these infections is purely clinical at the onset of illness, for the usual laboratory findings in blood, urine etc., are not of diagnostic value. The aetiological diagnosis is based on virus isolation. The following specimens are essential for establishing a diagnosis.

(1) A sample of blood collected as early in the illness as possible *i.e.*, within 4 days of onset. (2) A sample of blood collected 14 days after the onset of illness or at the time of discharge from hospital or at the last clinic attendance, whichever is earlier. (3) Cerebrospinal fluid and throat swab, collected at the onset. (4) Faeces specimens collected for three consecutive days, soon after the onset of illness. Virus is isolated by inoculating the prepared faecal suspension into primate epithelial cell cultures. Cytopathogenic changes *i. e.*, morphological changes in the cells and the cell sheet are usually demonstrable microscopically within 2 to 7 days of inoculation. The cytopathogenic agent is confirmed to be a virus by 2 or 3 consecutive passage in tissue culture. The viral isolate is then identified as poliomyelitis or Coxsackie virus by the neutralization test against specific antisera. If it is not neutralized by specific sera, neutralization tests are done with the patient's acute and convalescent sera to establish the aetiological role of the virus to the illness. Identification of the virus is also carried out.

It is possible under present day conditions to isolate and type the poliomyelitis virus from patients in 3 to 7 days. Laboratory confirmation is possible in 95% of paralytic poliomyelitis cases whereas virus isolation is positive only in 40 to 50% of nonparalytic poliomyelitis cases. This resulted in the search for other viruses in these cases and the search had been quite fruitful as shown by the enlarging group of intestinal viruses.

Treatment: The treatment is purely symptomatic as no effective virucidal therapeutic agent has yet been found. The management of poliomyelitis cases though arduous and prolonged does provide very encouraging results. The virus is excreted for long periods by patients and hence attention to personal hygiene may curtail the spread of infection in the community.

Prophylaxis: Since specific prophylaxis is not available against most of these infections, hygienic measures and quarantine are recommended. The efficacy of the latter is not proved. The former though efficacious, is rather difficult to enforce particularly in children who are more susceptible to these infections.

Poliomyelitis: The most ancient of these infections is the only one for which a prophylactic vaccination is available now. The Salk vaccine as produced in recent times is quite safe. It contains all three types of polio virus completely inactivated with formaldehyde. It significantly reduces the incidence of paralytic polio during an epidemic in the vaccinated community. The vaccine is administered parenterally in three doses, the interval between the first and second

dose being 6 weeks and that between the 2nd and 3rd dose 6 to 9 months. The vaccination does not prevent infection with poliomyelitis virus but only reduces the incidence of paralytic poliomyelitis. The conditions prevailing in tropical countries do not seem to warrant vaccination against poliomyelitis but it may be worthwhile considering immunisation of foreigners coming into these regions as they seem to pick up paralytic poliomyelitis more readily while in the tropics. An attenuated live oral polio vaccine is being worked out but it has not had as extensive a field trial as the Salk vaccine.

Human gamma globulin in doses of 0·15 c.c. per lb. of body weight is recommended as a prophylaxis to pregnant women in the presence of epidemic polio and also for laboratory workers when exposed to the risk of infection.

Summary

An attempt has been made to describe the clinical manifestations of illnesses of intestinal viral aetiology. No adequate attempts have been made to study these infections in the tropics. The laboratory diagnosis of these infections is described.

TABLE I

POLIOMYELITIS

Incubation period: **5 to 35 days**

Incidence: All ages susceptible, children are mostly affected in tropical countries.

	Clinical type	**Signs and symptoms**	**Pathogenesis**
1.	Silent infection	Nil	Virus present in faeces only.
2.	Minor illness	Fever, headache, drowsiness, vomiting, constipation and muscle pain.	Virus present in blood and faeces.
3.	Non-paralytic poliomyelitis	Fever, headache, vomiting, sorethroat, drowsiness, and pain in the neck and back.	Virus in blood and faeces, evidence of C. N. S., invasion with virus.
4.	Paralytic poliomyelitis	Fever, headache, vomiting, sorethroat, drowsiness, and pain in the neck and back, with paralytic signs and symptoms.	Virus in blood, and faeces C. N. S. involvement present.

Children: Minor illness, nonparalytic phase, paralytic phase.

Adults: Minor illness very mild or not evident and the illness develops with clinical evidence of central nervous system involvement.

TABLE II
COXSACKIE VIRUS

Incubation period: 4 to 10 days

Multiple cases in families.

Name of Illness	Herpangina	Aseptic meningitis	Minor illness	Myalgia	Epidemic pleurodynia
Age	Under 10	All ages are susceptible			
Symptoms	Fever, vomiting, sorethroat, headache and muscle pain. Pain of diaphragmatic region of chest and abdomen in epidemic pleurodynia.				
Signs	2 to 12 ulcerations in the throat, soft palate, anterior pillar of fauces, tonsils, and posterior pharyngeal wall. These start as papules and proceed to vesiculation and ulceration.	Meningeal signs			

TABLE III
EXANTHEM DISEASE

Incubation period: 3 to 7 days

Incidence Children and adults

Symptoms Fever, sorethroat, headache, stomachache, abdominal cramps chills and muscle pains.

		Children	Adults
Signs	I Skin Rash	Yes	Yes
	(i) Onset	During or after the fever.	After the fever only.
	(ii) Type	Generalised over face, chest wall and extremities.	Scanty usually over abdomen only.
		Macular, blotchy when confluent.	Macular, not confluent.
	(iii) Duration	2 to 4 days	24 to 36 hours

	Children	Adults
II Adenopathy	Few enlarged glands seen in some cases.	Not a feature.
III Severity of Illness	Mild ; patient ambulant.	Severe with prostration and pain in the eye.

Table IV

EPIDEMIC EXANTHEM ASSOCIATED WITH MENINGITIS

Age: Chiefly children under 10 years; more than one case in the family.

Complaint: Fever, severe headache, nausea and vomiting.

Signs: Macular rash ; lasting for a few hours or days.

Mouth lesions ; grey or white dots on buccal mucosa opposite molar teeth.

Slight generalised lymphadenopathy.

Signs of meningitis.

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Managing Editor.

ASSOCIATION NEWS

Nilgiri District Branch

The monthly meeting of the association was held on 29th March 1958 at the Lawley Institute, Ooty. Dr. G. R. Gopalakrishnan addressed the members on "Ophthalmology in General Practice."

Tiruchy Branch

A monthly meeting of the association was held on Saturday the 22nd March 1958 in the premises of the Medical Association Buildings, Tiruchy. Dr. L. S. Ramachandran, M.B.B.S., B.S.SC., D.T.M. presided.

Dr. K. Ramachandran, M.S., Madurai addressed the members on "Surgical Aspects of Chronic Splenomegaly".

Dr. T. V. Ranganathan, M.B.B.S., L.O. (Mad.), Z.O., (vien.), D.O. (Lond.) gave a short account on his recent visit to Western Countries.

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A monthly meeting of the association was held on Sunday the 13th April 1958 in the premises of the Medical Association Buildings, Tiruchy. Dr. L. S. Ramachandran, the President presided.

Dr. K. P. Ganesan, M.D., Hony. Physician, Govt. Wenlock Hospital and Reader in Medicine, Kasthurba Medical College, Mangalore addressed the members on "Some Syndromes of the Cervical Spinal Cord".

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A meeting of the Association was held on Friday the 25th April 1958 in the premises of the Medical Association Buildings, Tiruchi. Dr. L. S. Ramachandran presided.

Dr. T. S. Chelvakumaran, B.A., M.B.B.S. M.S. (Mich.) Professor of Anatomy, Madurai Medical College, Madurai addressed the members on "Development of the Pharynx and the Pharyngeal Derivatives".

Salem Branch

The Silver Jubilee Celebrations of the Salem Branch was held on Saturday the 29th March 1958 at the Cooperative Rest House Hall, Salem. The foundation stone of the Association Building at Five Roads, (Alagapuram Road) was laid by Dr. D. V. Venkappa, President of the Indian Medical Association. Dr. S. R. Rajaram, Chairman, Silver Jubilee Celebration Committee welcomed the guests. The celebrations was inaugurated by Dr. D. V. Venkappa. After a short speech by Dr. M. Santosham, President of the Madras State Branch of I. M. A., Dr. B. A. Rajarathnam proposed a vote of thanks. The Scientific Session was inaugurated by Dr. P. Arunachalam. Dr. R. Subramanyam, BSC., M.D., M.R.C.P. Dr. B. Ramamurthy, M.S. F.R.C.S. and Dr. M. V. Chari, M.R.C.P., D.T.M. & H., addressed the members on "Management of Coronary Thrombosis", Treatment of Convulsions and "Respiratory diseases in children" respectively.

At the Annual Meeting held on 29th March, 1958, the following Office-Bearers for the year 1958–1959 have been elected.

President : Dr. S. Krishnamoorthi Rao.

Vice-President : Dr. M.B. Yuvaraja Singh

Hony. Secretary :
Capt. V. Raghavendra Rao.

Hony. Joint Secretary :
Dr. T. Narayanasamy.

Hony. Treasurer :
Dr. K. V. Dhanakoti Nayudu.

Members of the Executive Committee :

1. Dr. K. Jayaramachandran
2. Dr. S. Kannan
3. Dr. Kumari U. B. Lakshmi.
4. Dr. S. Arthanari
5. Dr. K. Govindarajulu.

Representative to the Central Council :
Dr. K. R. Hariharan.

Alternate Member to the Central Council :
Dr. T. S. Shanmugasundaram

Representatives to the State Council :

1. Dr. S. Valeeswaran.
2. Dr. T. Narayanaswami.
3. Dr. K. Govindarajulu.